

Research Article

Early Age at Menarche and Wheezing in Adolescence: The 1993 Pelotas (Brazil) Birth Cohort Study

Gary Joseph*, Ana Maria Baptista Menezes and Fernando C. Wehrmeister

Post-Graduate Program in Epidemiology, Federal University of Pelotas (UFPEL), Brazil

***Corresponding author**

Gary Joseph, Post-Graduate Program in Epidemiology, Federal University of Pelotas (UFPEL), Maréchal Deodoro street, 1160, 3rd floor, Pelotas, Brazil, Tel: 53-813-853-99; Email: garyj2010@hotmail.fr

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Abstract

Objective: To evaluate the effect of menarche before 11 years of age on the incidence of wheezing/asthma in girls 11 to 18 years of age.

Methods: The study sample comprised 1,350 girls from a birth cohort that started in 1993 in the urban area of the city of Pelotas, southern Brazil; this cohort was followed until 18 years of age. We assessed wheezing by the question, "Have you ever had wheezing in the chest at any time in the past?" from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Early menarche was defined as occurring before 11 years of age. We estimated the cumulative incidence of wheezing excluding from the analysis all those participants who reported wheezing before age of 11 years. We performed the chi-square test to assess the association between ever wheezing and independent variables. Poisson regression models with robust variance were used to estimate cumulative incidence ratios.

Results: The average age at menarche in the cohort girls was 12 years (95% CI: 11.1–12.1). The prevalence of early menarche before 11 years of age was 11% (95% CI: 9.7–12.3). The cumulative incidence of wheezing from 11 to 18 years of age was 33.5% (95% CI: 30.9–36.0). The crude association between ever wheezing in adolescence and early menarche before age 11 was 1.19 (95% CI: 0.96–1.48). After adjusting for early childhood and contemporaneous variables, no significant association for early menarche before 11 years of age and wheezing during adolescence was found (CIR: 1.18; CI95%: 0.93–1.49).

Conclusion: Early menarche before 11 years of age is not associated with an increased risk of wheezing during adolescence.

ABBREVIATIONS

BMI: Body Mass Index; CI: Confidence Interval; CIR: Cumulative Incidence Ratio; FAPERGS: Foundation for Research Support of the State of Rio Grande do Sul; ISAAC: International Study of Asthma and Allergies in Childhood; OR: Odd Ratio; PNAD: National Household Sample Survey; SUS: National Health System; WHO: World Health Organization.

INTRODUCTION

Asthma is the most common chronic disease in children and adolescents. It has a major impact on quality of life and increases the demand for health care [1,2]. Clinical manifestations of asthma include recurrent episodes of wheezing, shortness of breath,

dry cough, and chest discomfort or tightness especially at night or early morning hours [3]. It is a potentially serious condition if not properly treated [3,4]. The pathogenesis of asthma is multifactorial and involves environmental, sociocultural, ethnic and genetic factors [2,5].

Asthma affects around 300 million people worldwide, accounting for more than 250,000 deaths [1,6]. About one-third of those affected are younger than 18 years [6]. Data from the World Health Organization (WHO) have shown that, in Western Europe, the incidence of asthma has doubled over the past 10 years [7].

Asthma is also a major public health concern in Brazil. It is the fourth leading cause of hospitalizations in the Brazilian National

Health System (SUS) (2.3%) and the third leading cause among children and young adults [8]. Data from the 2012 National Household Sample Survey (PNAD) showed annual percent increases of asthma in children and adolescents in many macro-regions in Brazil [9].

Several theories have been postulated to explain the phenomenon of increasing incidence and prevalence rates of wheezing/asthma in children and adolescents, but there is no consensus [10,11]. Because there is no gold-standard approach for the diagnosis of asthma, different studies are not comparable making it difficult to further understand the increasing prevalence of this condition [10,12]. In light of that, the term wheezing/wheeze has been used in several epidemiological studies as a proxy for “asthma” in children and adolescents and is the preferred term for this condition in the International Study of Asthma and Allergies in Childhood (ISAAC) [2,13,14]. In the present study, wheezing and wheeze are used interchangeably.

Among a number of factors described to be associated with the development of asthma/wheezing in female adolescents is the age at menarche [13,15]. Menarche is the first menstrual cycle that usually occurs two to three years following puberty in female adolescents, around 11–13 years of age [16]. Although there is no consensus [17,19], some authors define early menarche as occurring before 11 years of age [13,20].

The average age at menarche fell from 16–17 years to under 13 years over the past 100 years [21–23]. Studies conducted in South Korea showed that, from 1920 to 1925, the average age at menarche was 16.9 years, and from 1980 to 1985, it fell to 13.8 years [21]. Data from WHO (1995) show that, in Brazil, the average age at menarche was 12.2 years in adolescents from families with high socioeconomic status and 12.8 in those from poor families in the city of São Paulo in 1978 [24]. In a 2010 study, in Brazil, Martínez et al. reported that the average age at menarche was 12.4 years [25].

The reasons for the decline in age at menarche are multifactorial and involve both genetic and environmental factors [19,21,23]. Some investigators have argued that the decline in the average age at menarche could be associated with increasing wheezing/asthma incidence in adolescent girls [15,17,18].

In view of data showing a decline in age at menarche and increasing asthma incidence in some countries, we conducted a study with participants from the 1993 Pelotas birth cohort to examine this relationship.

METHODS

The 1993 Pelotas cohort comprised children born between January 1 and December 31, 1993 in the city's five maternity hospitals to mothers living in the urban area of Pelotas. Of 5,265 eligible infants, 16 were lost or refused to participate in the study. The remaining 5,249 infants were included in the original sample. Further details about the methods of the 1993 birth cohort can be found in previous publications [26,27].

Perinatal follow-up consisted of daily visits to the five maternity hospitals. Mothers were asked to fill a standard questionnaire to collect information on demographic, socioeconomic, behavioral, and reproductive characteristics, health care and family health conditions.

We followed the original cohort participants at ages 11, 15 and 18 years, with a follow-up rate of 87.5%, 85.7%, and 81.3% respectively. Information was collected on socioeconomic and behavioral characteristics, family health conditions, nutritional status, smoking, physical activity, puberty characteristics, and health conditions among others. Home interviews were carried out at ages 11 and 15. At age 18, the adolescents were asked to fill out questionnaires and underwent a series of assessments at the study site.

The study outcome—ever wheezing—was examined for the three follow-ups. We assessed wheezing by asking the question, “Has <NAME> / have you ever had wheezing in the chest at any time in the past?,” from the ISAAC questionnaire. This information was reported by the mothers at age 11 and by the adolescents at ages 15 and 18 (Annexes 1,2 3). We analyzed ever wheezing as a dichotomous (yes/no) variable. From the variables “cumulative incidence of wheezing”, we generated a new variable—cumulative incidence of wheezing in adolescence—based on the reporting of wheezing in the follow-ups at ages 15 and 18.

For the assessment of the association between ever wheezing and age at menarche, we excluded from the analysis all those girls who reported wheezing before 11 years of age.

We assessed age at menarche based on information collected in the follow-ups at ages 11, 15 and 18 years by asking the following questions, “Have you ever had a menstrual period?,” with yes/no answer options, and then if yes, “How old were you when you had your first menstrual period?,” reported in years and months. This information was reported by the mother at age 11, and by the adolescents at ages 15 and 18. From the variable age at menarche collected at the three follow-ups (2004, 2008 and 2011), we generated a new variable—continuous age at menarche until age 18. This variable was then dichotomized as before 11 years and greater or equal to 11 years.

Information was collected on potential confounders in the perinatal follow-up – maternal smoking during pregnancy (yes/no); birth weight (<2500 g, ≥2500 g); in the 2004 follow-up – family history of allergy/asthma or bronchitis (yes/no); household income into quintiles (the first quintile represented the poorest); self-reported skin color (white, black, other); nutritional status (body mass index [BMI]-for-age z-score by the WHO growth charts) [28]; adolescent smoking assessed by the following question “Have you ever tried cigarette smoking, even one or two puffs?,” with yes/no answer options, physical activity into quartiles (the first quartile represented the lowest level of activity); and in the 2008 follow-up – Tanner stages (five stages of pubic hair development).

For assessing potential selection bias, we carried out a comparative analysis of selected perinatal and household income variables collected in the 2004 follow-up between the sample of adolescents enrolled in the study at age 11 and those from the original cohort using the chi-square test. We compared the following variables: gestational age according to the method of Dubowitz [29], maternal parity, maternal BMI at the beginning of pregnancy according to WHO [30], type of birth, family history of allergy/asthma or bronchitis, household income and birth weight of the adolescents.

Descriptive analyses were performed on all independent

variables. Any association with incidence of wheezing from 11 to 18 years was assessed using the chi-square test. We used Poisson regression models with robust variance to estimate crude and adjusted cumulative incidence ratios (CIRs) according to the variable age at menarche before 11 years old. Two models were constructed for adjusted analyses. Model 1 was adjusted for household income, family history of allergy, maternal smoking during pregnancy, birth weight and self-reported skin color. Model 2 was adjusted for model 1 by adding the variables nutritional status, physical activity, smoking, and Tanner stages. With a sample size of 1004 people, considering a 5% significance level, the statistical power for the present analysis was 92%. All statistical analyses were conducted using Stata software version 12.1.

The 1993 Pelotas Birth Cohort Study was approved by the Ethics Committee of the Federal University of Pelotas. A free informed consent form was signed before participating in the follow-ups by all participants (mothers and adolescents).

RESULTS

Of 2,609 female infants in the original cohort, information was collected for 2,235 in the follow-up at age 11. Of these, 1,350 were eligible to participate in the study, as they reported no wheezing ever. The cumulative incidence of wheezing from 11 to 18 years of age was 33.5% (95% CI 30.9–36.0) (Figure 1). Of the 1350 girls eligible in the study, information's on age at menarche were missing for about 3.4%. The average age at menarche in the cohort girls was 12 years (95% CI 11.1–12.1). The prevalence of menarche before 11 years of age was 11% (95% CI 9.7–12.3).

(Table 1) shows the general characteristics of our sample and the cumulative incidence of wheezing from 11 to 18 years of age according to the main exposure variables, i.e., menarche before 11 years. Most adolescents reported white skin color (66.3%) and nearly half reported a family history of allergy, asthma or bronchitis. Almost one-third of the mothers reported smoking during pregnancy. About 3.5% of the girls reported smoking experience at age 11, and only 3% were in the first Tanner stage of pubertal development at age 15. The cumulative incidence of wheezing in girls with menarche before age 11 was 40.3%.

Table 2 shows a comparative analysis of our sample with the original cohort. We found no statistically significant differences except for family history of allergy, asthma or bronchitis ($p = 0.002$).

In (Figure 2,) the cumulative incidence ratio (CIR) between ever wheezing in female adolescents and early menarche before 11 years was 1.19 (95%IC: 0.96-1.48). After adjusting for early childhood and contemporaneous confounding variables (model 2), no significant association for early menarche before 11 years of age and wheezing during adolescence was found (CIR: 1.18; CI95%: 0.93-1.49).

DISCUSSION

This study examined the relationship between age at menarche and ever wheezing from 11 to 18 years of age in female adolescents from the 1993 Pelotas birth cohort study, and found no significant association between menarche before age 11 and the incidence of wheezing during adolescence, both in the crude

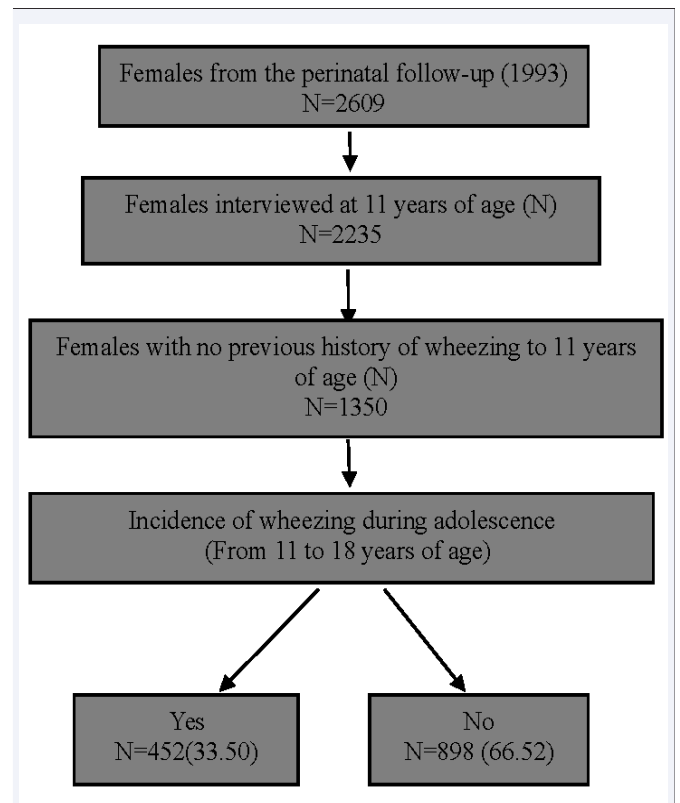


Figure 1 Sample size for the analysis between age at menarche before age 11 and the incidence of wheezing during adolescence. The 1993 Pelotas (Brazil) birth cohort study.

Table 1: Description of the variables studied and the cumulative incidence of wheezing (from 11 to 18 years) according to the main exposure variables of the study. The 1993 Pelotas (Brazil) birth cohort study.

	Description	Cumulative inc. of wheezing (from 11 to 18 years)
Variables	N (%)	N (%)
Birth weight (g)*£		p=0.874
>=2500g	1101 (89.7)	405 (33.5)
<2500g	127 (10.3)	46 (32.9)
Adolescents skin color†		p=0.064
White	892 (66.3)	279 (31.3)
Black	150 (11.2)	54 (36.0)
Other	303 (22.5)	116 (38.3)
Family income(quintile of minimal wage)†		p=0.114
Q1(poorest)	237 (17.6)	80 (33.7)
Q2	285 (21.1)	95 (33.3)
Q3	266 (19.7)	102 (33.4)
Q4	276 (20.4)	96 (34.8)
Q5(richest)	286 (21.2)	79 (27.6)

Maternal smoking during pregnancy £		p=0.807
No	838 (68.2)	308 (33.70)
Yes	392 (31.8)	144 (33.03)
BMI standard (z-score according to WHO)†		p=0.058
<-2	33 (2.5)	5 (15.1)
-2 to +2	1215 (90.2)	415 (34.2)
>+2	99 (7.3)	30 (30.3)
Adolescent smoking †		p=0.042
No	1290 (96.3)	425 (32.9)
Yes	49 (3.7)	23 (46.9)
Physical activity(quartile of minimal wage)†		p=0.754
Q1 (less active)	320 (24.5)	99 (30.9)
Q2	334 (25.7)	116 (34.7)
Q3	335 (25.8)	114 (34.0)
Q4 (more active)	311 (24.0)	103 (33.1)
Tanner' pubic hair stage		p=0.607
Stage I	36 (2.9)	12 (33.3)
Stage II	141 (11.4)	57 (40.4)
Stage III	485 (39.3)	169 (34.8)
Stage IV	455 (36.8)	150 (33.0)
Stage V	118 (9,5)	40 (33,9)
Family history of allergy, asthma or bronchitis †		p=0,755
No	706 (52.8)	233 (33.0)
Yes	630 (47.2)	213 (33.8)
Menarche <11 years of age ¥		p=0,119
No	1162 (89.0)	392 (33.7)
Yes	144 (11.0)	58 (40.3)

£Variables collected during the perinatal visit †Variables collected during the 2004 visit

‡Variables collected during the 2008 visit

¥ Variable collected during the 2004, 2008 and 2011 visits *Variable with maximum missing values (n=122) p: p-value of the Pearson X² test

Abbreviations: BMI: Body Mass Index; WHO: World Health Organization

Table 2: Comparative analysis of the sample of adolescents selected to 11 years in relation to the original cohort. The 1993 Pelotas (Brazil) birth cohort study.

Variable	Selected sample (N%) to 11 years	Original cohort N (%)	p-value
Birth weight (g) £			0.363
<2500g.	140 (10.4)	299 (11.3)	
>=2500g.	1208 (89.6)	2338 (88.7)	
Maternal smoking during pregnancy £			0.190
Yes	436 (32.3)	909 (34.4)	
No	914 (67.7)	1736 (65.6)	
Family history of allergy, asthma or bronchitis †			

Yes	630 (47.2)	1165 (52.4)	0.002
No	706 (52.8)	1056 (47.5)	
Family income(quintile of minimal wage)†			0.056
1st (poorest)	237 (17.6)	449 (19.9)	
2nd	285 (21.1)	477 (21.1)	
3rd	266(19.7)	447 (19.8)	
4th	276(20.4)	444 (19.6)	
5th (richest)	286 (21.2)	444 (19.6)	
Maternal gestational age in weeks (Dubowitz) £			0.107
<37 weeks	102 (7.7)	238 (9.2)	
>=37 weeks	1229 (92.3)	2351 (90.8)	
BMI at the beginning of pregnancy (Kg/m²)£			0.308
<18,5	103 (7.8)	204 (7.9)	
18,5 to <25	896 (67.8)	1781 (69.1)	
25 to <30	254 (19.2)	469 (18.2)	
>=30	68 (5.2)	122 (4.7)	
Mother's delivery £			0.539
Unique	1325 (98.1)	2603 (98,4)	
Multiple	25 (1.9)	42 (1,6)	
Maternal parity £			0.903
Primiparous	469 (34.7)	924 (34.9)	
Multiparous	881 (62.3)	1721 (65.1)	

£ Variables collected during the perinatal visit † Variables collected during the 2004 visit

p: p-value of the Pearson X² test

Abbreviations: BMI: Body mass index

as in the adjusted analysis taking into account confounding factors.

Few studies have examined the association between early menarche and incidence of wheezing and they have used different definitions of age at menarche [13,15,17-20].

In a cohort study in Australia, Burgess et al. reported that age at menarche (<11 years) was not associated with asthma onset during adolescence (OR 0.99; 95% CI 0.73–1.33) or during adulthood (OR 0.96; 95% CI 0.70–1.30) [31]. In another cohort study, Galobardes et al. found that girls reporting later age at menarche (>12 years) were more likely to develop atopic asthma (RR 1.37; 95% CI 1.03–1.81) [32].

Nevertheless, other studies have shown different results [13,18,20]. In a study conducted in Mexico, Herrera et al. showed a significant association between menarche (≤11 years) and wheezing during adolescence (OR 1.31; 95% CI 1.01–1.73) [13]. Similarly, Macsali et al., in a cohort study including 3,335 women aged 27–57 years, in Norway, found a significant association between early age at menarche (<11 years) and incidence of asthma (OR 1.80; 95% CI 1.09–2.97) [20].

In a United States cohort study, Salam et al. followed a sample

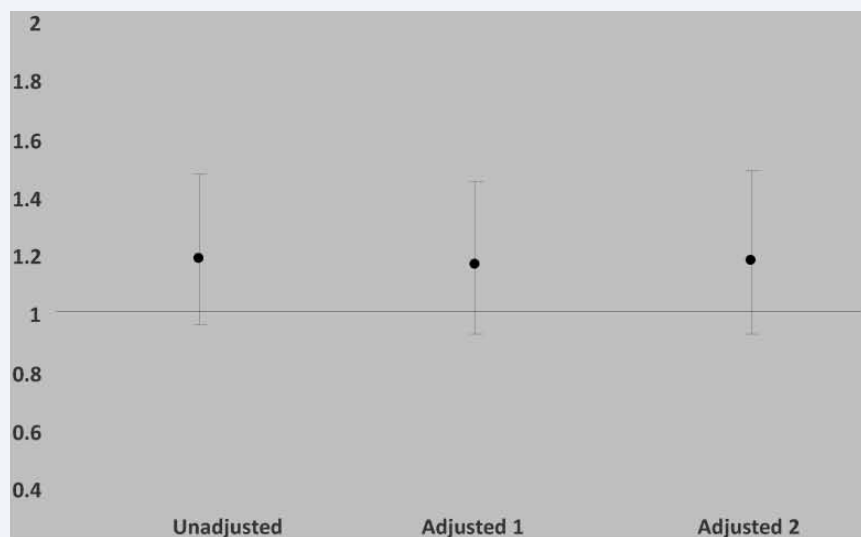


Figure 2 Unadjusted and adjusted analyses between menarche before age 11 and the incidence of wheezing during adolescence. The 1993 Pelotas (Brazil) birth cohort study.

of 905 women and found that women with menarche before 12 were twice as likely (OR 2.08, 95% CI 1.05 -4.12) to develop asthma in adult life compared to those with menarche at 12 years of age or older [18]. However, it should be noted that had a low response rate ($\approx 50\%$) [18].

Several hypotheses of the mechanisms involved have been proposed to explain the relationship between early menarche and incidence of asthma in adolescence or young adulthood. Some authors have argued that female hormones play a major role in the development of asthma [13,15]. Girls with early age at menarche are exposed to higher levels of estrogen and progesterone at an earlier age, which would increase their risk of asthma [13,15,18,20, 33]. Many cells with immune regulatory function have estrogen receptors and may produce a shifted immune response toward allergic and chronic conditions such as asthma [34]. Other studies have suggested a role of progesterone in the development of asthma [35,36]. Progesterone increases expression of β -2 receptors which results in reduced bronchial smooth muscle relaxation [35,36], although the study of Barnes showed progesterone as a protective factor for wheezing [37]. The relationship between female hormones and asthma is complex, and further studies are needed to investigate it.

The *age at menarche* has declined considerably over the past 100 years [21,22] while the prevalence of wheezing/asthma in adolescents has increased [7,9]. The main reasons for this decline in age at menarche include environmental toxins, socioeconomic conditions, perinatal health, nutritional status, maternal smoking, ethnicity, among others [19,21,23]. Besides family history of allergy or asthma, these are other known risk factors for wheezing/asthma during adolescence [38,39].

A number of limitations of this study need to be considered. Among these, we highlight the fact that we used the question on “wheezing in the past” from the ISAAC questionnaire to assess the presence of asthma. According to the literature, this symptom can be considered a proxy for the diagnosis of asthma especially during childhood and adolescence with little possibility

of memory bias [6,14]. Furthermore, the ISAAC questionnaire has been validated and used in several countries including Brazil [14]. Another limitation of the study is referred to the intensity of wheezing episodes that occur in these adolescents. Mild and occasional attacks of wheezing could not have been remembered or even noticed by the mothers of teenagers. Therefore, the actual incidence of wheezing in adolescents could have been underestimated in the study.

Age at menarche—the main exposure of this study—may be subject to recall bias. However, Must et al. showed that menarche is an important life event and not prone to bias [40].

Despite these limitations, the present study makes noteworthy contributions. It is one of few studies conducted in Brazil on this subject using data from a population-based birth cohort with high follow-up rates in its three waves and with information collected prospectively. Also, we highlight the high statistical power obtained for the present analysis. Moreover, information collected throughout childhood and early adolescence allowed to controlling for confounding factors in the analyses.

Further epidemiological investigations especially longitudinal studies with female adolescents may help better understand the relationship between age at menarche and the incidence of wheezing during adolescence.

IMPLICATIONS AND CONTRIBUTIONS

This is one of few studies conducted in Brazil to investigate the relationship between age at menarche and the incidence of wheezing during adolescence, using data from a population-based birth cohort, and showed no significant association between menarche before age 11 and the incidence of wheezing during adolescence, both in the crude as in the adjusted analysis for confounding factors. Further epidemiological investigations especially longitudinal studies are needed to assess the relationship between age at menarche and the incidence of wheezing during adolescence.

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